REMARKS / ARGUMENTS

1. No New Matter Has Been Added

No new matter has been introduced by way of this amendment. For each amendment made, proper support exists in the originally filed specification at the pages indicated.

2. Summary of Amendments

Claims 1 and 118 are amended. Claim 108 is canceled, and new claim 119 is added. Claims 101 - 107, 109, 118 and 119 are pending in the application. By amending claim 101, it is believed that all objections raised have been traversed, and the Applicants request that all objections be withdrawn.

3. Support for Amendments Within Specification

The specification makes reference to a "catheter" in various places, as recited in claim 101 and 118 as amended. For example, the description of Figure 2 at page 5, lines 24 and 25:

> Figure 2 illustrates the use of a medical catheter to position device accurately within a vein.

Also, at page 8, lines 10-14:

> The fibre may be positioned within a blood vessel, and this embodiment would allow analysis of a component of interest adsorbed from blood flowing through said blood vessel. Optionally, the step of positioning said fibre comprises guiding the fibre into position within the blood vessel using a catheter. Other areas in an animal in which the fibre may be positioned include....

Further, at page 12, lines 4 - 6:

> The positioning device itself may a catheter, for those applications where the fibre is guided into a blood vessel, such as a vein, or other tubular biological structures, as discussed in more detail below."

The descriptions of Figures 1 and 2 found on page 17 and of Figure 4 found on page 18 of the application provide a more detailed discussion of the use of such a catheter according to the invention.

The specification supports reference to the catheter for placement within an animal or animal tissue, and being immobilized during sampling as recited in claim 101 as amended. Specifically, support can be found at page 13, lines 24-26:

> Preferably the device is introduced to the tissue under study via a standard medical positioning device such as a catheter or microdialysis cannula.

Further, at page 17, lines 6 to 8 (emphasis added):

> Figure 1, part C, illustrates an embodiment comprising the extraction device alone with no support rod and no handle may be introduced to a blood vessel through a previously placed medical catheter 10...

Figure 2 also illustrates the use of the catheter, and reference is made to page 5, lines 24 and 25, as well as page 17, lines 21 to 26:

> Figure 2 illustrates the use of a medical catheter to position device accurately within a vein. [page 5]

> Figure 2 shows the use of a medical catheter 10 passing through the skin 20 and vein wall 18 to position the extraction device 9 with PRN 12 inside a vein 22 with blood flow 16 past the exposed extraction phase 4. In this position the extraction device has been fully depressed through catheter so that the extraction phase is fully exposed to flowing blood outside of catheter. PRN 12 is still accessible to allow for flushing to ensure patency of the catheter. [page 17]

In respect of Example 1 on pages 38 (line 29) to page 39 (line 5), it is clear that the catheter employed in the dogs under study was immobilized in place over a lengthy sampling period (emphasis added):

> Figures 23 to 26 show the results of the use of the device by the catheter sampling method described above, for a pharmacokinetic study in dogs. In this case dogs were dosed with diazepam at time 0:00. Multiple samplings were performed from a catheter over the ensuing 12 hours. Calibration was by comparison to results from an external calibration in whole blood similar to that shown in Figure 12. Also shown is a comparison to results obtained by multiple blood draws over the same time period, with conventional sample preparation and analysis as described in the description of the prior art. "

The specification refers to a device having a plurality of fibres for positioning at the same location in the animal or animal tissue, as recited in new claim 119. For example, Figure 4 provides illustration of this embodiment, and is described at page 5. line 27:

> Figure 4 is a schematic of a catheter with multiple coated fibres.

Also at page 18, lines 14 to 18:

> Figure 4 shows modifications to the device and a housing for multi-fibre sampling using a commercial catheter. Fibres 24, 26 and 28 are coated by coating 30, 32 and 34 respectively, which can be the same type of coating to increase capacity of the device, or preferentially each fibre having different highly selective coatings, such as antibodies designed to recognized only defined components of interests in a living animal.

Thus, it is believed there is adequate support in the specification for the claim amendments and the new claim now put forth.

4. Claim Rejections - 35 USC § 112

Claim rejections raised under 35 USC § 112 on pages 2 and 3 of the Action have been traversed by removal of the offensive terms "an attachment region" and "permanently attachable".

5. Claim Rejections - 35 USC §102

That Applicant believes that the claim rejections raised on pages 3 to 5 under 35 USC §102 are traversed by the amendments and arguments in support thereof now put forward. The amendments made to claim 101 emphasize features that are not taught or suggested in any prior art reference. Each of the remaining claims depends from claim 101, and thus each dependent claim also overcomes the objection raised under 35 USC §102.

5.1 The Objection of Anticipation by U.S. 5,691,206

The Examiner alleges that claims 101, 107, 109 and 118 are rejected under 35 USC 102 as being anticipated by U.S. 5,691,206. The Examiner points to the following passages of the '206 patent: col 2, lines 10-21; col 5, lines 10-15; col 3, lines 52-65; and figures 2 and 3. Nowhere in any of these passages, or elsewhere in the '206 patent is there mention of the use of a catheter for positioning the coated end of the fibre within an animal or animal tissue. These limitations have now been included in claim 101, and thus should traverse the anticipation objection raised on the basis of this reference to this claim, as well as to claims 101, 107 and 109. This reference does not teach or suggest a way in which sampling can be done in an animal or animal tissue. To the contrary, the passage from column 6 (line 60) to

column 7 (line 10) of the '206 patent, describing possible applications of this technology does not refer to use in an animal or animal tissue, but largely provides examples relating to flowing water systems, such as groundwater samples.

5.2 The Objection of Anticipation by Frerot *et al.* 1997

Frerot *et al.* was applied by the examiner as an anticipatory reference against claims 101, 107 and 118. The amendments made to claim 101 traverse this objection.

Frerot *et al.* does not teach that a catheter be used as a positioning device for guiding the coated end of a fibre into an animal or animal tissue, as now recited in claim 101. Frerot *et al.* teaches extrusion of the contents of an insect's gland from the gland and onto a fibre, the fibre being equipped with a Supelco™ SPME holder. The extrusion of the insect's gland's contents onto the fibre is done by a laboratory technician applying pressure on the abdomen of the insect until the contents of the gland comes out (see second last paragraph on page 340 of Frerot *et al.*). There is no implication that the fibre be positioned within the insect itself using a catheter. Nor is there any implication that the holder would fit inside the insect or any other animal or animal tissue. The Supelco™ "holder" referred to by Frerot *et al.* is simply a sheath that allows a user to hold or transport the fibre without directly contacting the fibre itself. Such a holder is not equivalent in any way of a positioning device such as a catheter.

The appropriate catalogue number for the Supelco™ SPME holder for manual sampling, as may be the most comparable product to the one used by Frerot *et al.*, is SPME Fibre Holder Catalog Number 57330-U. The dimensions of this holder are approximately 0.8 cm in diameter and 13.5 cm in length, similar in appearance to a ball-point pen. The SPME holder is rigid, and has blunt ends. Such a holder is not the equivalent of a positioning device that could guide a fibre into position within an animal or animal tissue. In fact, to insert such a holder into an animal would require that a large orifice be bored into the animal in advance of the insertion. Nor could the Supelco™ SPME holder be considered the equivalent of a catheter. Catheters are flexible, and capable of movement within an animal or animal tissue. The Supelco™ SPME holder is intended for protection of the fibre, for example, during transport, and requires the large dimensions and rigidity in order to carry out this function. Thus, it is clearly not the equivalent of a positioning device as now described in claim 101.

As amended, claims 101, 107 and 118 are not anticipated by the teachings of Frerot *et al.*

6. Claim Rejections - 35 USC §103

That Applicant believes that the claim rejections raised on pages 5 to 10 under 35 USC §103 are traversed by the amendments and arguments in support thereof now put forward. The amendments made to claim 101 emphasize features that are not taught or suggested in any prior art reference either alone or in combination with any other reference.

The limitation found in previous claim 108, that the positioning device comprises a catheter, has been included in claim 101 as amended, and thus the Applicant will primarily address the obviousness objection raised to claim 108 on page 6 of the Action. The Applicant believes that a prima facie case of obviousness has not been established with respect to previous claim 108.

6.1 Prima Facie Case of Obviousness Has Not Been Established

According to MPEP 2143, the three basic criteria for establishing prima facie obviousness are 1) suggestion or motivation in the references themselves or generally that the references be modified to combine the teachings; 2) reasonable expectation of success; 3) a teaching or suggestion that the combination be made, and the expectation of success must both be found in the prior art (not in the Applicants' disclosure). These criteria are referred to herein as the first criterion, the second criterion, and the third criterion.

6.1.1 First Criterion

The first criterion for establishing prima facie obviousness has not been met. There is no suggestion or motivation in either the '206 patent (Pawliszyn) or Frerot *et al.* that the device be changed in such a way as would incorporate a catheter used by Van Bockel (the '180 patent).

The '206 patent is aimed primarily at applications relating to manual sampling of fluids, such as groundwater streams. A syringe-style housing is depicted, which acts as a housing to protect the fibre during deployment and transport, and can later be used for insertion of a sample into an analytical instrument. There is no implication in this document that there is a need to position a fibre within an animal or animal tissue. Further, there is no implication that

sampling from the exact same site repeatedly, or immobilizing the housing itself for repeated sampling would have any advantage. At col 5 (lines 15 and 16) of the '206 patent, it is stated:

> The microextractor can be directly inserted into the fluid stream.

which conjures up the image of a technician leaning over a flowing fluid source, dipping the device into a fluid stream, and removing it again after a set period. There is no motivation provided to alter such sampling by using a catheter.

The Frerot *et al.* reference places the sample onto the fibre by squeezing the contents of an insect's abdomen, and rubbing the fibre in the extruded contents for 5 minutes, as specified on page 340:

> The gland was extruded by a gentle pressure on the abdomen and the entire fibre surface was gently rubbed on the tegument of the glandular area for 5 min.

While Frerot *et al.* employ the Supelco™ SPME holder (as discussed above), this is not the equivalent of a positioning device, but rather acts as a housing to protect the fibre. There is no motivation found in Frerot to insert the fibre into the insect to be sampled. Indeed, each insect would only be able to contribute to one sample, and thus multiple sampling from the same area of an insect would not be a possibility. Frerot does not provide motivation to create a device that would be positioned into an insect (or any other animal or tissue) using a catheter.

The '180 patent of Van Bockel does not relate to SPME, but is simply an example of the use of a medical catheter for placement of a device within the body. In this document, the device is introduced into the body and is pushed through the catheter to remain as an indwelling device, for use in conjunction with an endoprosthesis. It is clear that the catheter is removed from the body once the device is inserted, and it is also emphasized that no wires need extend from the device at all. It is simply placed permanently into the body through the bore of the catheter, after which time the catheter is removed. At col. 1 lines 66 to col 2, line 6 it is stated:

> A device according to the present invention can be introduced into a human or animal artery, especially into an aneurysmal sac. The pressure sensor can provide pressure related data that can be transmitted to a receiving means outside the human or animal body by means of the transponder. Wireless transmission of the data has the

> advantage of eliminating the need for wires extending from the pressure sensor to the skin of an animal or human.

There is no suggestion in the '180 patent that the catheter remain in place so that the device described (or any device) can be removed periodically through an indwelling catheter. At col 2, lines 27-29, it is stated:

> The device can be pushed through the same catheter into position as the endoprosthesis, which is used for treatment of the aneurisms if necessary.

There is no motivation in the '180 patent to adapt this technology to use a fibre that is insertable into the catheter.

6.1.2 Second Criterion

The second criterion for establishing prima facie obviousness has not been met. Specifically, there was no reasonable expectation of success for success if the device of either the '206 patent or Frerot *et al.* be used in conjunction with a catheter, as taught in the '180 patent.

If the device of the '206 patent was to be inserted through a catheter in the manner taught by the '180 patent, there could be no success. The initial problem would be that the device taught in the '206 patent is too bulky to fit in a catheter. The device comes complete with a housing surrounding the fibre. Nowhere in the '206 patent is there an implication that an embodiment of the device be used without the housing, or that the housing be small and flexible enough to fit in the bore of a catheter. Even if the catheter was considered as a substitute for the housing described in the '206 patent, then the entire catheter would need to be used for transporting the fibre from the sampling site to the analytical device (one of the advantages of the housing taught in the '206 patent. This would be awkward and bulky for a field technician, especially if multiple samples were obtained at a site.

If the device of Frerot *et al.* was to be inserted through a catheter in the manner taught by the '180 patent, there would be no possibility of success. As with the '206 patent, the problem of the Supelco™ SPME holder being the size of a ball-point pen would be the initial problem to be overcome. Because the subject of Frerot *et al.* is an insect, the second hurdle would be to insert a catheter properly into the abdomen of an insect for sampling. Frerot et al does not

imply that the fibre could be removed from the Supelco™ SPME holder and inserted into a catheter prior to sampling.

Considering the above comments, clearly there can be no expectation of success by combining either the '206 patent or the Frerot *et al.* teachings with the catheter implantation of the device taught by the '180 patent.

6.1.3 Third Criterion

The third criterion for establishing prima facie obviousness has not been met, in particular, there is no teaching or suggestion that a *combination* be made so that the prior art SPME be adapted for use in an animal or animal tissue by employing a catheter. Neither the '206 patent nor Frerot *et al.* discuss the possibility of inserting the fibre into an animal or animal tissue. the '206 patent is directed primarily to extraction from flowing water sources by direct insertion of a fibre into a fluid, such as a "water matrix sample" (col 4, lines 27-34 of the '206 patent), a "fluid stream"(col 5, line 16 of the '206 patent).

The applicant has reviewed the three applied references: the '206 patent, the Frerot *et al.* reference and the '180 patent, and has failed to see any passage that suggests combining a fibre and housing with a catheter as a positioning device, or indeed any other positioning device that permits periodic sampling of an animal or animal tissue at a consistent site.

6.2 Unobvious Advantages of the Invention over Prior Art

Employing a catheter to position the fibre has advantages that are expounded upon in the specification, for example at pages 21 (line 23) to page 22 (line 2) of the instant specification, which reads (emphasis added):

> In the embodiment, an animal being monitored does not need to be tethered, but rather can carry a device for automatically moving probes in and out of a catheter, cannula or other sampling port at prescribed times. After sampling the device would hold the probes for retrieval and quantification at a later time. This embodiment would have similar advantages to the microdialysis system in terms of **reduced human intervention and hence reduced sampling errors, with the additional advantage that animals in a study would be less restricted and stressed, and experiencing a more normal environment. This would reduce stress impacts on the integrity of the results.**

Further, an advantage of using the invention with a catheter as a positioning device, as opposed to a typical rigid SPME holder of the type described by Frerot *et al.* is described at page 16 (lines 25-27):

> When constructed of the stainless steel wire described below the extraction device is quite flexible. It will follow curves in a vein or catheter and normally resume a straight configuration when removed.

On the basis of the amendments and the rationale put forth above, it is requested that the obviousness objection raised to the claims be revisited and withdrawn.

6.3 Remaining Objections Raised Under 103

A number of other objections were raised to claims other than claim 108, specifically: a) to claims 102 and 103 (combining the '206 patent with Frerot et al. and Basta (U.S. 6,730,096); b) to claim 106 (combining the '206 patent with Frerot et al, and Quay et al (U.S. 6,287,521); c) to claim 104 (combining the '206 patent with Frerot et al., and Colburn et al (U.S. 2003/0183758); and d) to claim 105 (combining the '206 patent with Frerot et al., and Riviere et al (U.S. 2003/0180954).

Each of these claims now depends from claim 101 as amended, which includes the limitations previously found in claim 108. Thus, the arguments put forward above with respect to claim 108 should be adequate to render other objections on the basis of obviousness moot. Full analysis of each objection, and why a prima facie case of obviousness has not been established are thus not included here However, briefly, the applicant wishes to point out to the examiner the following differences between the applied art and the instant invention as now claimed in claim 101.

Regarding the examiner action regarding MALDI-related reference (Colburn at al.), although application of MALDI is common, the format of SPME-MALDI is unique since it incorporates the extraction step, among other distinctions now found in claim 104 as it depends from 101.

Regarding the calibration standard reference (Riviere at al), the use of calibration standards are common, the calibrant according to the embodiment of the invention claimed in claim 105 is delivered to the investigating system via the extraction phase, not by previous spike of the

investigated system. This approach to calibration is compatible with in-vivo monitoring since only small amount of calibrant enters the investigated tissue rather then contamination of the whole investigated system. Riviere et al. measures permeation of a membrane, not the concentration of analytes.

The remaining references of Quay et al. and Basta do not teach or suggest the limitations now recited in the claims. It is believed that the obviousness objections raised to claims 102-103, 104, 106 and 108 are rendered moot and should thus be withdrawn.

7. Request for Continued Examination

A Request for Continued Examination is being filed concurrently as of today's date. The fee for RCE is included.

Applicant believes that no additional fee is due with this submission, but nevertheless authorizes the Commissioner to debit any required fee from or credit any overpayment to Deposit Account No. 501593, in the name of Borden Ladner Gervais LLP.

It is submitted that this application is in condition for allowance. Early and favorable consideration is respectfully requested.

Respectfully submitted,

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